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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/741,534	12/19/2003	Alain Baron	18528.675 / 0218-UTL-9	5134

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Intellectual Property Department
Amylin Pharmaceuticals, Inc.
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EXAMINER	
STOICA, ELLY GERALD	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
07/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/741,534	BARON ET AL.	
	Examiner	Art Unit	
	Elly-Gerald Stoica	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-11,13-20,22-29,31-38 and 40-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-11, 13-20,22-29, 31-38,40-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application/Claims

1. In the amendment, filed 05/14/2007, Applicant cancelled claims 3, 12, 21, 30, and 39, amended claims 1-2, 10-11, 19-20, 28-29, and 37-38 and added claims. Currently, claims 1-2, 4-11, 13-20, 22-29, 31-38, 40-56 are pending.

Specification

2. The objection to the specification is withdrawn as consequence of the amendment by the Applicant.

Withdrawn claim rejections

3. The rejection of claims 1-2, 4-11, 13-20, 22-29, 31-38, and 40-45 under 35 USC § 102, and of the claims 1-2, 4-11, 13-20, 22-29, 31-38, and 40-46 under 35 USC § 112, written description requirement, is withdrawn in the view of the amendment.

Maintained and new claim rejections necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-2, 4-11, 13-20, 22-29, 31-38, and 40-46 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

At pages 11 –12 of the Remarks, applicants argue that: ..."the scope of the genus of GLP-1 compounds is viewed in the context of the claimed method, and the disclosure of species within the genus is understood by those skilled in the art based on the scope of teachings related to the claimed methods. Within this context, any suitable GLP-1 compound may be useful in the invention, e.g., useful as agents to treat nephropathy, treat End Stage Renal Disease (ESRD), improve endothelial function, reduce proteinuria, or slow progression of glomerulosclerosis. Extensive exemplary embodiments of known GLP-1 compounds with known activity in activating a GLP-1 receptor are discussed in the specification." "...the Specification provides numerous GLP-1 species that are representative of the claimed genus. In addition, the specification provides for a wide-range of deletions, substitutions, and insertions may be made to the amino acid sequences of GLP- 1 mutants. Specification, for example, at page 6, line 18 - page 13, line 19. The present application discloses numerous GLP-1 sequences and provides modified forms of the GLP-1". This argument has been fully considered but is not deemed persuasive because the claims still mention agonists or analogs or derivatives of GLP-1. However, the specification does not provide a conserve sequence that is linked to the functional properties of the GLP-1 members of

the genus claimed and such they read upon anything that might treat nephropathy. Therefore, the rejection is maintained.

5. Claims 1-2, 4-11, 13-20, 22-29, 31-38, and 40-45 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons of record. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The arguments of the Applicant were carefully studied but not considered persuasive. Specifically, as iterated in the previous Office action, the specification discloses that "an analog" includes any polypeptide and which has at least about 50% sequence identity with an amino acid sequence encoding a base molecule whether or not including insertions, substitutions, extensions, or deletions. Such analogs may comprise conservative or non-conservative amino acid substitutions (including non-natural amino acids. An "agonist analog," is an analog that exhibits at least one characteristic or action of the base molecule, preferably having potency better than the base molecule, or **within five orders of magnitude (plus or minus) of potency compared to the base molecule**. A "derivative" includes any base molecule or analog having a chemical modification within, attached, linked to, or associated with the molecule. Such chemical modifications can include internal linkers (e.g., spacing or structure-inducing) or appended molecules, such as molecular weight-enhancing molecules (e.g., polyethylene glycol (PEG), polyamino acid moieties, etc.), or tissue targeting molecules. Finally, a "variant" includes any modification to the base molecule not encompassed in the terms "analog" and

"derivative" (p4-5). However, the specification does not teach any functional variant, fragment, or derivative of the GLP-1 other than the full-length sequence of SEQ ID NO: 1. The Applicant is pointing to the Seq. Id. 2-11 and contends that they constitute adequate written description for a genus of GLP-1 molecules that share a 90% identity with Seq. Id. No.: 1. Even if considering this argument, which is not applicable for all the Seq. Id. Nos. 2-11 since some of the sequences contain more than three possible mutation sites (and the Seq. Id. No.: 1 is 31 amino acids long, the scope of the genus claimed is still considered to broad. At page 14 of the Remarks, applicants argue: "...the law provides that experimentation is not necessarily undue simply because it is complex, if the art typically engages in such experimentation." This argument has been fully considered but is not deemed persuasive because the real issue here is that the scope of the claims is to broad, given the definition on analogs and variants and agonists provided in the specification (see supra). Based on that definition one may envision, contrary to the arguments of the applicants, even a new class of compounds since they are defined only by function. There is no working example regarding the method claimed while employing any of the members of the genus for treating nephropathy. There is also a lack of guidance with respect to the conserved structure needed for the activity claimed, the working example being limited to GLP-1. For these reasons it still maintained that the amount of experimentation needed to establish that the species of the GLP-1 90% identity genus having the activity claimed and which can be used for treatment of nephropathy is undue. The specification is rather enabling with regard to agonist analogs or derivative having GLP-1 activity.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 19-27 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons of record. The Applicant's arguments were carefully considered but not found persuasive. Specifically, the example provided in the specification with regard to the term "endothelial function " and mentioned in the amendment as clarifying the claim is very specific and limiting example of one of the functions of the endothelium. As claimed, the "endothelium function" is still considered indefinite since the endothelium has other multiple functions and thus the meets and bounds of the claims could not be determined. Also unclear is who needs improvement of the endothelial function and how is it possible to determine the effective amount short of dissecting the patient.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-2, 4-11, 13-20, 22-29, 31-38, 40-46, and the new claims 47-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coolidge et al. (WO

01/89554, 11/29/2001), in view of Guitard et al. (US 2001/0016586, 08/23/2001). The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The claims are drawn to a method for preventing or treating a subject having nephropathy (claims 1 and 2) or for preventing progression to ESRD (claims 10-11), or of improving endothelial function in a subject in need thereof (claims 19 and 20), or of reducing proteinuria in a patient (claims 28 and 29), or for preventing or slowing progression of glomerulosclerosis (claims 37 and 38), comprising: administering to an individual in need of such treatment an effective amount of a compound which is a GLP-1 or a biologically active agonist, analog, derivative, variant, or fragment of it. Each of the main claims is further limited by dosage, rate of administration and mode of administration as follows:

- from about 0.001 pmol/kg to about 20nmol/kg (claims 4, 22, 31, and 40).
- from about 0.001 µg/kg/dose to about 1.0 µg/kg/dose (claims 5, 23, 32, and 41).
- the dose should achieve a plasma level of at least 40pg/ml (claims 6, 24, 33, and 42).
- the administration is parenterally (claims 7, 25, 34 and 43).

- the intravenous dose is from about 0.1 pmol/kg/min. up to about 10 pmol/kg/min (claims 8, 26, 35, and 44)
- the subcutaneous dose is from about 0.1 pmol/kg/min to 75 pmol/kg/min (claims 9, 27, 36, and 45).

The newly presented claims 47-56 further limit the claims to compounds that are 95% or 100% identical to the GLP-1 of Seq. Id. No.: 1.

Coolidge et al. teach a method of treatment, using GLP-1, of an individual with cardiac abnormalities consistent with ischemic heart disease (p28, lines 5-18). The continuous administration doses taught are 0.1-10 pmol/kg/min, or from 0.5-50 pmol/kg/min, for subcutaneous administration (p 19, lines 22-26), which are well within the limits of the claims of the instant application. The parenteral administration route of the instant claims could be any of the intravenous or subcutaneous routes of Coolidge at al. The biological properties of the GLP-1 are intrinsically related to its structure and its function is inherent. As correctly pointed out by the Applicant, Coolidge did not specifically teach treating nephropathy, treating End Stage Renal Disease (ESRD), improving endothelial function, reducing proteinuria, or slowing progression of glomerulosclerosis with GLP- 1. However, the GLP-1 molecule of the invention of Coolidge et al. would bind and exert its action irrespective of the condition sought to be treated.

GLP-1 and analogs were previously known in the art for their use to treat diabetes, as acknowledged by the Applicant in the specification and in the Remarks (e.g. U.S. Pat. 5,574,008-which teaches a method of treating diabetes with GLP-1 analogs). The

definition of the ESRD, end-stage renal disease, according to the OnLine medical dictionary (27 Sep 1997) refers to "a patient with inadequate renal function to support life. Individuals with end-stage disease must rely in kidney dialysis or peritoneal dialysis to survive. End-stage renal disease may be caused by a number of problems including diabetes, sickle cell disease, hypertension and congenital renal disease (polycystic kidney disease). (Published at the Centre for Cancer Education, University of Newcastle uponTyne, 1997. The Centre for Cancer Education.)

Guitard et al. teach the use of GLP-1, as a hypoglycemic agent, in nephropathies, peripheral angiopathies, hypertension, microangiopathic changes, diabetes and insulin resistance.

At page 22 of the Remarks, applicants argue: "...the Office has failed to establish a prima-facie case of obviousness because there would have been no reasonable expectation of success, at the time the invention was made, in combining the teachings of Coolidge et al. with Guitard et al."; "Without proper motivation and a reasonable expectation of success, the claims are improperly rejected under 35 U.S.C. § 103." This argument has been fully considered but is not deemed persuasive because Coolidge treats ischemic heart disease with GLP-1 and thus inherently treats the same components of the vascular system that are in play in nephropathies (i.e. veins and arteries). The first target in the treatment would have been the endothelium lining these vessels and this is the situation also for nephropathies which can be induced by ischemic events in the kidney. Therefore, the expectation of success is reasonable when combined Guitard et al. teachings of using GLP-1 in nephropathies. Therefore,

contrary to arguments of the Applicant, which are trying to attack the teachings individually, when considering the subject matter as a whole, it would have been *prima facie* obvious to one of skill in the art to modify the methods taught by Coolidge et al. in the diseases taught by Guitard et al., with a reasonable expectation of success. Motivation to do so comes from the etiology of the end stage renal disease, which is linked to insulin metabolism deregulation that may be controlled by GLP-1, as taught by Coolidge et al. and the well known at the time that the invention was made as presented in the evidentiary reference *supra*. More over, methods of treatment of diabetes with GLP-1 analogues were successfully used at the time that the invention was made (as evidentiary mentioned) so that the success was actually almost guaranteed.

Conclusion

7. No claims are allowed.

8. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elly-Gerald Stoica whose telephone number is (571) 272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER